PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Camurati-Engelmann Disease (CED) via *TGFB1* Gene Sequencing (Test #787)

Brief Description of Clinical Features: Camurati-Engelmann disease (OMIM#131300) is characterized by hyperostosis of the long bones and the skull, proximal muscle weakness, severe limb pain, a wide-based, waddling gait, and joint contractures. Facial features such as frontal bossing, enlargement of the mandible, proptosis, and cranial nerve impingement resulting in facial palsy are seen in severely affected individuals later in life (Wallace & Wilcox *GeneReview* 2010). Rare manifestations include anemia, anorexia, hepatosplenomegaly, decreased subcutaneous tissue, atrophic skin, hyperhidrosis of the hands and feet, delayed dentition, extensive caries, delayed puberty, and hypogonadism (Gupta & Cheikh *Endocr Pract* 11:399–407, 2005).

Genetics: Camurati-Engelmann disease is inherited in an autosomal dominant manner with reduced penetrance. *TGFB1* is the only gene known to be associated with CED. *TGFB1* encodes transforming growth factor beta-1 (TGF-β1), a large precursor molecule and a multifunctional peptide that controls proliferation, differentiation, and other functions in many cell types. TGF-β1 preprotein contains a signal peptide of 29 amino acids that is proteolytically cleaved. TGF-β1 is further cleaved after amino acid 278 to form latency-associated peptide (LAP) and active TGF-β1. LAP dimerizes with interchain disulfide links at Cys223 and Cys225. TGF-β1 can be secreted as an inactive small latent complex that consists of a mature TGF-β1 homodimer non-covalently associated with an LAP homodimer. The majority of pathogenic *TGFB1* mutations in individuals with CED lead to single amino-acid substitutions near the site of interchain disulfide bonds between the LAP homodimers. Three mutations in exon 4 (p.Arg218Cys, p.Arg218His, p.Cys225Arg) account for ~80% of the total mutations observed in CED (Campos-Xavier et al. *Hum Genet* 109:653–658, 2001). These mutations may disrupt dimerization of LAP and binding to active TGF-β1, leading to increased active TGF-β1 release from the cell (Janssens et al. *J Biol Chem* 278:7718–7724, 2003; Kinoshita et al. *Am J Med Genet* 127A:104–107, 2004).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *TGFB1* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also sequence any single exon (Test #100) in family members of patients with a known mutation, or to confirm research results ($190).

Reference Sequences: **Genomic: NC_000019.9** **mRNA: NM_000660.4**
Protein: NP_000651.3 **mRNA and Protein: CCDS 33031.1**

Indications for Test: Candidates for this test are patients with clinical and radiographic findings consistent with CED and family members of patients who have a known *TGFB1* mutation.

Sensitivity of Test: This test is predicted to detect disease mutations in >90% of individuals with a clinical diagnosis of CED (Janssens et al. *Nat Genet* 26:273–275, 2000; Kinoshita et al. *Nat Genet* 26:19–20, 2000; Campos-Xavier et al. *Hum Genet* 109:653–658, 2001; Mumm et al. *Am J Hum Genet* 69S:593, 2001; Wallace et al. *Am J Med Genet* 129A:235–247, 2004; Janssens et al. *J Med Genet* 43:1–11, 2006).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page four of the Requisition Form.

Prices: **Sequencing of *TGFB1* gene** **$ 620**

CPT Codes:

Sample Ascertainment x1	83890 $ 30	DNA Isolation x1	83891 $ 40
Amplification x9	83898 $170	Sequencing x9	83904 $250
Separation x1	83894 $ 40	Interpretation/Report x1	83912 $ 90

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12).

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